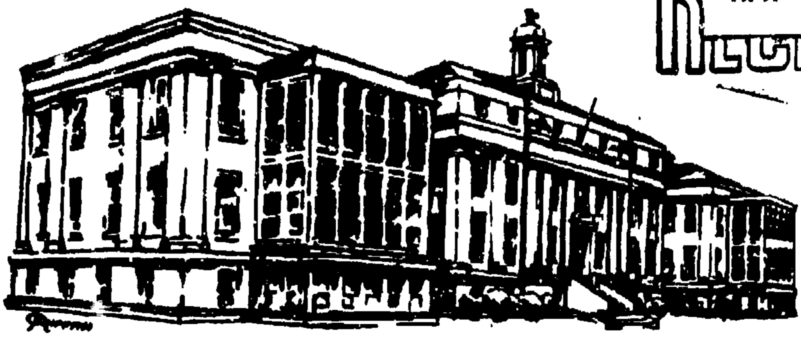
Multiple Infections in Acute Respiratory Diseases.

III. Natural Immunity to, and Interdependence of, Eleven Etiological Agents in Naval Recruits: An Analysis of Serological Data.

Christine Trautwein and Earl A. Edwards

April 1972



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Seroconversions caused by microbial agents in blood specimens from Great Lakes Naval recruits for a period from 1965-1968 were examined to determine the existence of interdependence among infection by 11 microbial agents. Serological rises in antibody titer to adenovirus and N. meningitidis were found simultaneously in the same men, much more frequently than would be expected by chance. Because of their simultaneous appearance, it is difficult to assign a casual role. No interdependence was found among the other agents. A surplus of individuals with no infection with any agent was observed. Conversely, those with any infection tended to have multiple infections. This clustering of infections in particular individuals may indicate differences in stress reactions to recruit training.

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MULTIPLE INFECTIONS IN ACUTE RESPIRATORY DISEASES

III. NATURAL IMMUNITY TO AND INTERDEPENDENCE OF ELEVEN ETIOLOGICAL AGENTS IN NAVAL RECRUITS: AN ANALYSIS OF SEROLOGICAL DATA

By

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Research Project Report MF 12.524.009-4013B, Bureau of Medicine and Surgery, Navy Department, Washington, D. C.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large. The use of commercially available products does not imply endorsement of, nor preference for, these products. The experiments reported herein were conducted according to the principles enunciated in "Guide for Laboratory Facilities and Care" prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council. The animal care facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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A longitudinal serological surveillance for microbial infections in Naval recruits has been in effect at Great Lakes since 1964. These serological data were analyzed to study the distribution of infectious experience among recruits. Combinations of seroresponses to 11 microbial agents were examined for evidence of either hypothesized interactions among agents (1) or the presence of differences in host factors affecting susceptibility. Such host factors which might be suggested by this analysis are differences in efficiency of the immunodefense system (2) and degree of stress due to social readjustment during recruit training. That personal differences may play a major role in determining the infectious experience of an individual was suggested by Voors et al (3). This analysis also provided an opportunity to examine the "ecological vacuum" phenomenon (4) which hypothesizes that organisms will fill the ecological niche left when other organisms are eliminated. These data also afforded the means to investigate the hypothesis that adenovirus deters subsequent infection with Mycoplasma pneumoniae (5).

MATERIALS AND METHODS

Since 1964, each month a company of recruits (70-100 men) has been randomly selected as a "surveillance" company. Such companies were then excluded from the routine acute respiratory disease (ARD) prophylaxis programs to serve as monitors of natural infection rates for those agents thought most likely to be found in recruit populations. All recruits in these companies were bled their 1st, 5th and 9th weeks of training. The serological tests performed and the number of sera tested are enumerated in Table I.

"Surveillance" companies were grouped so as to minimize the variables of time (a 4-year span was involved) and inter-company differences in infection rates. By such a grouping method, it was hoped, that all men in any given company cluster would have had approximately the same exposure rate to any one of the 11 agents. Infection rates for each infectious agent for each company of recruits were computed (a man was considered infected if his sera displayed a 4-fold rise in antibody titer [3-fold for ASO]). Those companies consecutive in time and having similar rates of infection for all 11 agents were grouped together, and a single infection rate for each agent for each company cluster was computed weighing each company in proportion to its number of men (Table II, & Fig. 1). Dates and numbers tested for each cluster are shown in Table III. From these rates, a rate for multiple agent infections to be expected purely by chance was computed for each company cluster. The expected rate was computed only for those combinations which actually occurred since the number of possible combinations of agents is 2048. Since only a fraction

of the sera samples were tested for all 11 agents (Table I), these expected rates were computed for a universe of six agents and a universe of 11 agents.

Methods for testing hypotheses. The possibility of one agent's deterring infection with a secondary agent or its absence predisposing a host to another agent was tested against the following criteria. Assuming the infections to be independent, the expected rates for combinations of agents were computed for company clusters as described above, and a comparison was made to the frequencies of combinations which actually occurred. The significance of this comparison was tested by computing the normal approximation to the binomial (6), and when a frequency was too small (≤ 5), a Poisson distribution for rare events was used to establish a rejection region ($p \leq .05$) for comparing the expected and observed frequencies. For example, in cluster III, four out of 291 men had M. pneumoniae and only M. pneumoniae. The percent expected to have this particular infection combination was computed thus: (% total population having M. pneumoniae) X (% not having influenza B) X (% not having adenovirus) ... etc., for all six infections. This expected percentage (3.3% in this case) was then multiplied by N = 291 to get the expected number, 9.66. A Poisson distribution was then used to determine the 95% confidence limits for the expected number (μ), given the observed number (x) = 4. In this case the upper limit was 9.153; thus the expected number of 9.66 was in the rejection region, and this particular infection combination was seen less than would be expected if the infections had occurred independently of each other, as was assumed in computing the expected number. In those instances where the observed number of an infection combination was >5, the normal approximation to the binomial was used to compute the probability of such a discrepancy between expected and observed frequencies. The Poisson distribution was chosen here (where the observed number ≤ 5) because the population considered was large and the percent infected with the low incidence infections was small relative to the total population. It is recognized that an assumption of a Poisson distribution here may cause an error in the rejection region if the distribution is not Poisson. Although this paper deals with numerous infection combinations with very low frequency, the results are not substantially influenced by a small number of men, rather trends involving numerous combinations are sought.

The hypothesis that adenovirus is a deterrent to infection with M. pneumoniae was analyzed in the following way: each company cluster was divided into 2 groups -- those who did show, and those who did not show a rise in antibody titer to adenovirus between the 1st and the 5th week of training. These 2 groups were divided into those with or without a subsequent rise between the 5th and 9th week of training in antibody titer to M. pneumoniae (Table IV). A Chi-square test was used to determine whether the group which had experience with adenovirus had fewer subsequent infections with M. pneumoniae. Where there were fewer than five cases in a group, the exact probability of the occurrence was computed.

Results: Within each company cluster, the expected and observed frequency of each combination of agents were compared. This comparison revealed a consistent surplus of the observed number of men with no infection whatever over the number expected by chance (Table V). Conversely, multiple infections showed a strong tendency to occur in certain individuals rather than single infections being evenly distributed among the populace. (These data are not shown because of the large number of multiple combinations). There did not appear to be any interdependence between influenza A and B, nor between influenza and other agents. Influenza A and B appeared separately and in combination only as frequently as could be expected by chance alone, considering the overall infection rate for the agents.

A strong positive relationship was observed between meningococcal infection and adenovirus infection, as measured by CF antibody responses. The number of individuals with this combination of infections consistently exceeded the frequency expected by chance (Table VI). Conversely, meningococcal infection appeared as the sole infection less frequently than expected (Table VII). In 72% of the cases with meningococcus and adenovirus, seroconversions to these two agents appeared in the same serum sample.

Both the examination of all companies aggregated and the examination of one company where the rate of M. pneumoniae infection reached 43% showed no deterrent effect of M. pneumoniae on other agents. Because of the low streptococcal infection (ASO) rate, it was impossible to test for the deterrence of M. pneumoniae on streptococcus as has been suggested (7).

The testing of the hypothesis that adenovirus deters infection with M. pneumoniae gave inconclusive results (Table IV). There was a significant difference in only 3 of 7 company clusters between the expected and observed frequencies. In those groups, the expected number of cases acquiring M. pneumoniae while having adenovirus was less than the observed frequency, $P = 0.05$, 0.03 and 0.005, for clusters II, V and VII, respectively.

The initial titer levels of the noninfected populations were compared to the initial titer levels of the infected population (Table VIII). The initial titer levels of the noninfected population were no higher, and some levels were lower, than the titer levels for the infected population (Fig. 2).

Discussion: Topley and Wilson, in discussing numerous epidemiological experiments of the 1920's (2), developed the concept of natural immunity. Natural immunity was the factor which allowed certain mice to survive lethal epidemics. The origin of this immunity was suggested to be one of the following: previous exposure to the agent with resulting production of antibodies; a pre-existing general antibody capable of adaptation to a particular agent; or the difference in an individual's ability to produce a new antibody to a challenging agent. In the current study, the surplus

of individuals who completely escaped any infection, while those with any differences in the immunity or immunizability of individuals, the origin of this immunity conceivably being any of the above. The greater immunity of certain individuals did not appear to be a result of their having had higher initial titer levels as shown in Table VIII and Fig. 2. Thus, it did not appear that their immunity was a result of recent exposure. This immunity to microbial infection persisted despite varying levels of overt disease, as evidenced by hospital admissions ranging from 2% during cluster I to 0.1% during cluster VII (8).

A possible explanation for a difference between noninfected recruits and recruits with multiple infection is their reaction to the stress of recruit training. An increase in the secretion of 17-hydroxycorticosteroids as a result of emotional strain could result in suppression of the immunologic responses and facilitate infection. That there are great personal differences in reactions to the stress of emotional readjustment and in resultant increases of 17-hydroxycorticosteroid secretions has been suggested by Voors (3) and Bourne (9). These personal differences may account for the basic differences between the infected and noninfected recruit.

Because of the low rates of infection for each agent tested (Table II), except adenovirus and *Neisseria meningitidis*, and the clustering of infections in particular individuals, it appears that the infection syndrome in recruit training may be more a product of personal differences than of an epidemic agent. Perhaps the stress of training may cause a host-parasite imbalance with indigenous "normal flora", or the stress, with its increase of 17-hydroxycorticosteroid secretion, may allow either infection with agents of low prevalence or the activation of a latent infection (10).

The strong correlation which was found between adenovirus and *N. meningitidis* was also reported by Artenstein et al (11). Since most (72%) of the cases with an infection of both agents acquired them during the same time period, it is difficult to establish a cause and effect relationship. Since specimens were taken at 1st, 5th and 9th weeks of training, there was a sizable spread of time during which the infection with the two agents could have occurred and still be first detected in the same specimen. Artenstein isclated both agents at the same time, and an effective adenovirus vaccine did not deter meningococcal infections. Thus, it does not appear that adenovirus predisposes one to meningococcal infections, although it had been proposed by Nichol (12) that virus attacks the respiratory mucosa and prepares the way for bacterial infection. The frequent simultaneous occurrence of the two agents and the lack of a clear casual relationship between them suggests the possibility that the individuals who are susceptible to either adenovirus or *N. meningitidis* are also susceptible to the other agent, and/or that the conditions for spread may be the same for both agents.

In addition to the relation between adenovirus and N. meningitidis, several other relationships were investigated. Influenza A and B were found to have no interdependence; this result supports the findings of both Crawford (1), who found no relation serologically and Rosenbaum (13), who found no relation on the basis of isolation. An examination of the hypothesis that adenovirus deters subsequent infection with M. pneumoniae suggests that further study of the relation might be worthwhile. Three of the seven clusters showed a deterrent effect, while the other four did not. A study of a large population with a higher rate of M. pneumoniae infection and a study of seasonal variation would give more definitive results.

This great frequency of multiple infections might be of interest to clinicians. Because of the likelihood of a multiple infection, a successful isolation of one agent should not preclude further examiniation for other possible agents creating the disease syndrome.

The observation of the levels of infection with these 11 agents afforded an opportunity to investigate the "ecological vacuum" theory. If, indeed the elimination of one agent created an ecological vacuum into which another agent is likely to enter, then one would expect to have seen the total infection rate remaining constant over time, with one agent replacing another as it is eliminated. An inspection of the total rates of infection (summing the infection rates for each agent) for each company showed widely fluctuating totals. Hence, either the ecological vacuum theory is invalid, or the 11 agents studied were not a representative enough sample of the agent spectrum to reveal the filling of the ecological vacuum.

SUMMARY

Seroconversions caused by microbial agents in blood specimens from Great Lakes Naval recruits for a period from 1965-1968 were examined to determine the existence of interdependence among infection by 11 microbial agents. Serological rises in antibody titer to adenovirus and N. meningitidis were found simultaneously in the same men, much more frequently than would be expected by chance. Because of their simultaneous appearance, it is difficult to assign a casual role. No interdependence was found among the other agents. A surplus of individuals with no infection with any agent was observed. Conversely, those with any infection tended to have multiple infections. This clustering of infections in particular individuals may indicate differences in stress reactions to recruit training.

Table I. Serological tests done on recruits for 11 infectious agents

Agent	Test	No. of men tested
Adenovirus	Complement fixation	2,207
Influenza A	Complement fixation	2,207
Influenza B	Complement fixation	2,207
Rhinovirus 1A	Neutralization	678
Rhinovirus 2	Neutralization	678
Rhinovirus 1B	Neutralization	678
Parainfluenza I	Hemagglutination-inhibition	678
Parainfluenza III	Hemagglutination-inhibition	678
Streptococcus	Anti-streptolysin O	2,207
Mycoplasma pneumoniae	Complement fixation	2,207
Neisseria meningitidis	Complement fixation	2,207

Table II. Percent infection for 11 infectious agents in recruit companies grouped by similar infection rates.

Agent	Company Cluster I	II	III	IV	V	VI	VII
Adenovirus	57.77	79.42	15.46	60.09	3.75	63.33	55.14
Influenza A	1.61	9.68	6.62	4.13	1.50	27.34	13.71
Influenza B	1.61	9.84	1.60	5.33	5.63	14.47	13.27
Rhinovirus 1A	17.85	8.58	5.31	12.09	11.45	9.91	8.59
Rhinovirus 2	51.49	11.04	25.00	11.90	12.50	13.33	41.54
Rhinovirus 1B	12.65	9.75	9.65	10.83	9.37	14.16	24.43
Streptococcus	1.34	8.53	5.08	6.60	7.14	6.94	6.61
Parainfluenza I	2.02	0.72	7.64	7.00	15.12	1.65	2.73
Parainfluenza III	8.00	6.96	8.16	14.00	6.00	9.09	6.88
M. pneumoniae	5.08	5.94	5.66	4.61	7.19	13.08	7.06
N. meningitidis	63.55	64.50	20.00	65.42	14.66	64.36	58.80

Table III. Recruit companies in training from 6 June 1965 to 3 October 1968 grouped together by similar infection rates.

Cluster number	Dates	Population with serology complete for 6 agents	Population with serology complete for 11 agents
I	6/28/65 - 10/25/65	61	14
II	12/14/65 - 5/12/66	318	101
III	6/15/66 - 10/11/66	291	128
IV	11/15/66 - 4/12/67	397	108
V	5/10/67 - 8/9/67	261	52
VI	9/6/67 - 1/11/68	301	86
VII	2/8/68 - 10/3/68	578	189

Table IV. Incidence of M. pneumoniae after infection with adenovirus in recruits compared to incidence after no infections with adenovirus (2 x 2 Chi-square).

Cluster number			Adenovirus infected	Adenovirus not infected	Significance
I	Subsequent M. pneumoniae	infected	1/0.6 *	0/0.4	N.S.
		not infected	134/134.4	91/90.6	
II	Subsequent M. pnuemoniae	infected	3/6.3	6/2.7	P = 0.05
		not infected	247/243.7	101/104.3	
III	Subsequent M. pneumoniae	infected	2/2.4	14/13.6	N.S.
		not infected	54/53.6	300/300.4	
IV	Subsequent M. pneumoniae	infected	1/1.3	2/1.7	N.S.
		not infected	34/33.7	44/44.3	
V	Subsequent M. pneumoniae	infected	0/3.1	23/19.9	P = 0.03
		not infected	41/37.9	245/248.0	
VI	Subsequent M. pneumoniae	infected	10/13.3	11/7.9	N.S.
		not infected	167/163.8	95/98.1	
VII	Subsequent M. pneumoniae	infected	5/11.2	16/9.8	P = 0.005
		not infected	306/299.8	257/263.3	

* observed/expected

N.S. = not significant

Table V. Expected and observed incidence of noninfected subjects among recruit companies (significance levels determined by a normal approximation to the binomial).

	Cluster number	Expected % noninfected	Observed % noninfected	
Population complete	I	14	23	0.04
for 6 infections	II	5	10	0.0001
	VI	6.5	8.6	*
	V	65	70	*
Population complete	II	3.5	8	0.015
for 11 infections	III	30	40	0.01
	V	37	48	*

*Not statistically significant

Table VI. Percent of recruits with serological evidence of infection with *Neisseria meningitidis*, adenovirus and other agents.

Agents	Cluster number*	Observed/ Expected	Significance
(Population complete for 11 agents)			
N. meningitidis, Adenovirus, Influenza A	II	6/2.5	P = 0.015
N. meningitidis, Adenovirus, Influenza	IV	43/18	P = <0.0001
N. meningitidis, Adenovirus, Rhinovirus 1B	IV	5.5/2	P = <0.0001
N. meningitidis, Adenovirus, Influenza A,B	VI	6/0.75	P = 0.05
N. meningitidis, Adenovirus, *M. pneumoniae*	VI	6/1.8	P = 0.05
N. meningitidis, Adenovirus,	VII	26.5/7.7	P = <0.0001
N. meningitidis, Adenovirus, Influenza A,B	VII	5.3/0.15	P = <0.0001
N. meningitidis. Adenovirus, Rhinovirus 1A	VII	1.58/0.59	P = 0.05
N. meningitidis, Adenovirus, Influenza A & Para III	VII	2/0.06	P = <0.001
(Population complete for 6 agents)			
N. meningitidis, Adenovirus, *M. pneumoniae*	I	5/1	P = 0.05
N. meningitidis, Adenovirus, ASO	II	2.2/0.39	P = 0.05
N. meningitidis, Adenovirus, *M. pneumoniae* Influenza A	IV	0.75/0.05	P = 0.05
N. meningitidis, Adenovirus, *M. pneumoniae* Influenza B	IV	0.75/0.07	P = 0.05
N. meningitidis, Adenovirus, Influenza A,B	VI	2.7/1.28	P = 0.03
N. meningitidis, Adenovirus, *M. pneumoniae*	VI	5.7/3	P = 0.006
N. meningitidis, Adenovirus,	VII	25/21	P = 0.016
N. meningitidis, Adenovirus, Influenza A,B	VII	4.7/0.5	P = 0.0000

*These men are grouped in clusters with the companies in each cluster having similar rates of infection for agents taken individually.

Table VII. Percent of recruits with serological evidence of infection with *Neisseria meningitidis* and other agents.

Agents	Cluster number*	Observed/ Expected	Significance
(Population complete for 11 agents)			
N. meningitidis, Rhinovirus 2	VII	1/4.4	P = 0.04
N. meningitidis only	VII	1.58/6.24	P = 0.0074
(Population complete for 6 agents)			
N. meningitidis, Influenza B	IV	0.25/1.17	P = 0.05
N. meningitidis, Influenza A	VII	1.2/2.7	P = 0.018

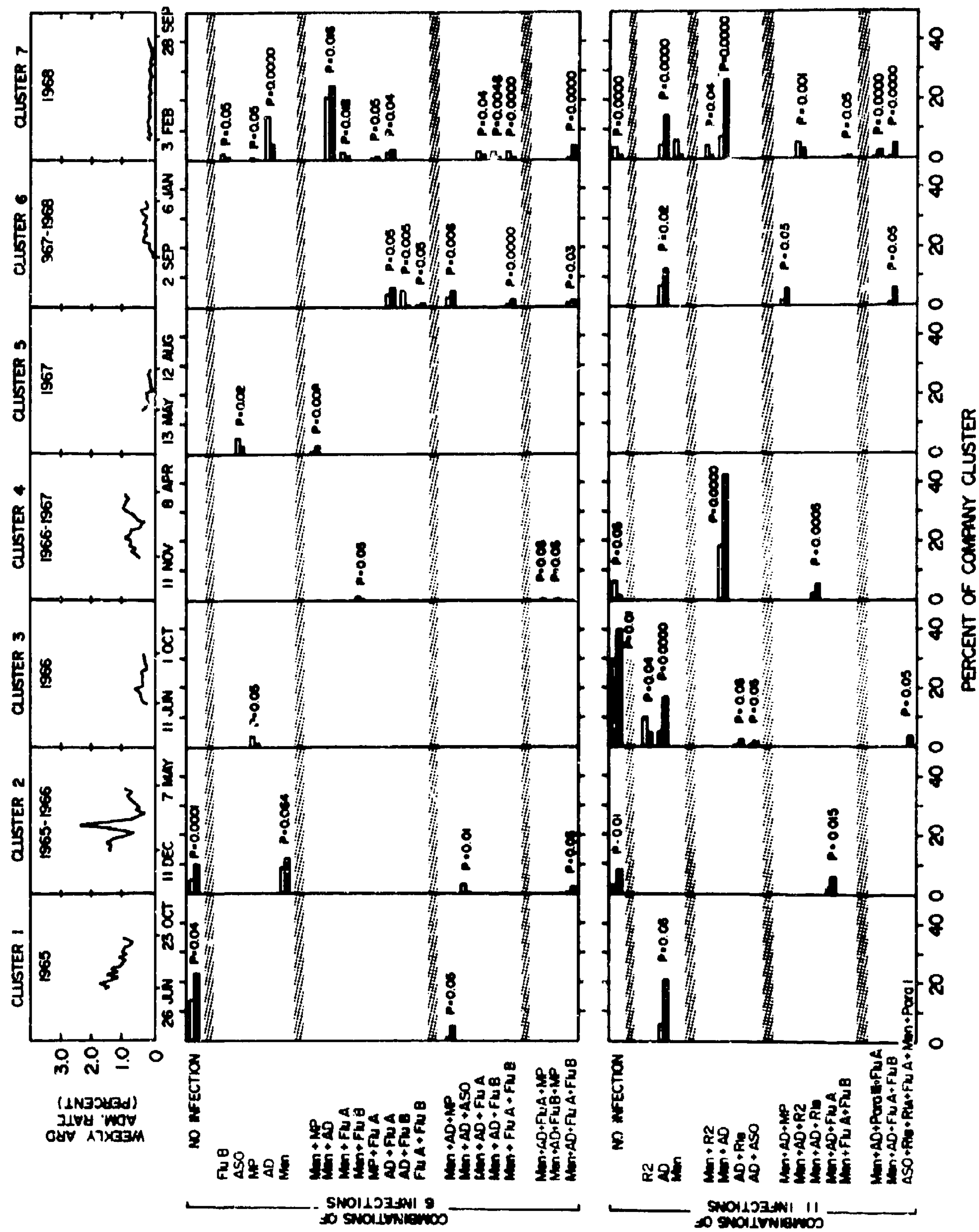
*The men are grouped in clusters with the companies in each cluster having similar rates of infection for agents taken individually.

Table VIII. Initial titer levels for recruits who may or may not have experienced an infection.

	No infection titer	infection titer
Adenovirus	7.12	5.1428
Influenza A	6.16	5.9588
Influenza B	6.4	5.1428
Mycoplasma pneumoniae	6.0	9.9584
Neisseria meningitidis	3.76	1.9674
Rhinovirus 1A	5.8944	11.6920
Rhinovirus 2	7.3684	7.5384
Rhinovirus 1B	7.588	9.8456
Parainfluenza I	25.0	57.0
Parainfluenza III	154.0	112.0
Streptococcus	160.0 Todd Units	182.0 Todd Units

Figure 1. Expected and observed frequencies for various combinations of agents in each of the 7 company clusters and chronologically corresponding weekly ARD hospital admission rates for Great Lakes Naval recruits. (Only those combinations where the difference between expected and observed frequencies is significant are shown.)

	= expected percent
	= observed percent
MEN	= *Neisseria meningitidis*
MP	= *Mycoplasma pneumoniae*
AD	= Adenovirus
R1A	= Rhinovirus 1A
R1B	= Rhinovirus 1B
R2	= Rhinovirus 2
Flu A	= Influenza A
Flu B	= Influenza B
ASO	= Antistreptolysin O
Para III	= Para Influenza III
Para I	= Para Influenza I


CLUSTER 1
1965
CLUSTER 2
1965-1966
CLUSTER 3
1966
CLUSTER 4
1966-1967
CLUSTER 5
1967
CLUSTER 6
1967-1968
CLUSTER 7
1968
WEEKLY ARD ADM. RATE (PERCENT)
COMBINATIONS OF 6 INFECTIONS
COMBINATIONS OF 11 INFECTIONS
NO INFECTION
Flu B
ASO
MP
AD
Men
Men + MP
Men + AD
Men + Flu A
Men + Flu B
MP + Flu A
AD + Flu A
AD + Flu B
Flu A + Flu B
Men + AD + MP
Men + AD + ASO
Men + AD + Flu A
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R2
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PERCENT OF COMPANY CLUSTER

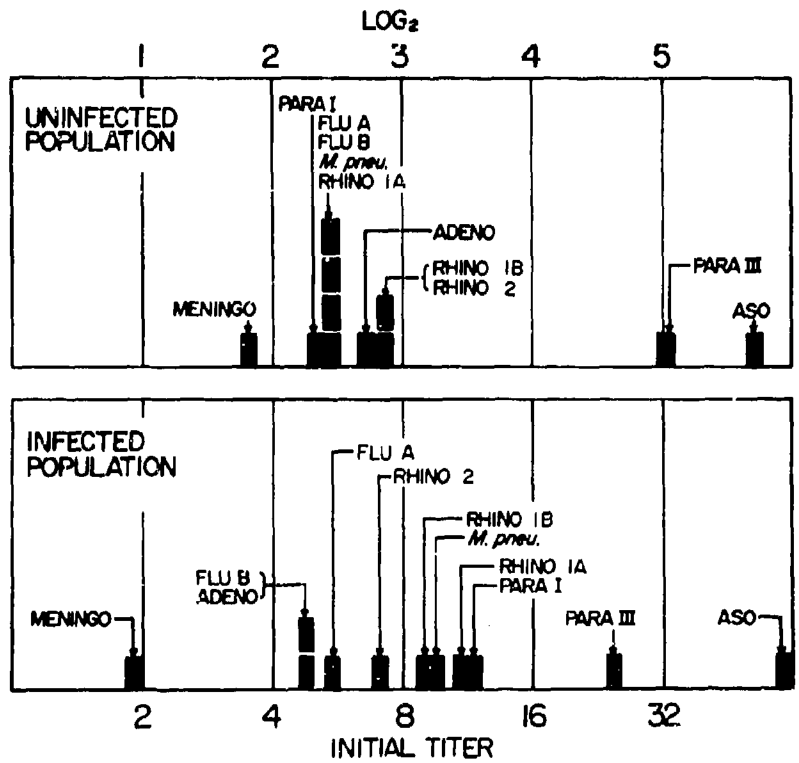

Figure 2. Initial titer levels to various agents for those recruits who subsequently became infected as opposed to those recruits who acquired no infection.

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